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COMMENTARY

EPIDEMIOLOGICAL EVIDENCE OF CHILDHOOD LEUKAEMIA AROUND NUCLEAR POWER PLANTS

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□ A few reports of increased numbers of leukaemia cases (clusters) in children living in the vicinity of nuclear power plants (NPP) and other nuclear installations have triggered a heated debate over the possible causes of the disease. In this review the most important cases of childhood leukaemia clusters around NPPs are described and analyzed with special emphasis on the relationship between the environmental exposure to ionizing radiation and the risk of leukaemia. Since, as indicated, a lifetime residency in the proximity of an NPP does not pose any specific health risk to people and the emitted ionizing radiation is too small to cause cancer, a number of hypotheses have been proposed to explain the childhood leukaemia clusters. The most likely explanation for the clusters is 'population mixing', i.e., the influx of outside workers to rural regions where nuclear installations are being set up and where local people are not immune to pathogens brought along with the incomers.

Key terms: childhood leukaemia, nuclear installations, ionizing radiation exposure.

According to the International Atomic Energy Agency database currently there are 435 nuclear power reactors in operation and 71 are under construction (IAEA 2013). In the cores of commercial reactors, which are the main component of a nuclear power plant (NPP), the nuclei of the fissile uranium-235 are gradually split apart under controlled conditions releasing great amounts of energy in the form of heat (nuclear fission of 1 kg of U-235 releases approximately three million times more energy than conventional burning of 1 kg of coal), some of which is then used to produce electricity; the total net installed capacity of the existing NPPs is 371,326 MW_e. During the fission of U-235 various radioisotopes are produced, many of which are discharged to the atmosphere through the plant's chimney ('stack emissions'). The plant staff and, to a lesser extent, people living in the vicinity of an NPP can be exposed to gamma radiation leaking from the reactor core, a number of beta- and gamma-emitters (such as Ar-41, C-14, Co-60, Cs-134 and Cs-137, H-3, I-131, Ir-192, Xe-133 and Xe-135) contained in the stack emissions as well as to non-ionizing electromagnetic fields surrounding the high-

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voltage electric power transmission lines which accompany every NPP (Fairlie 2010; Lane *et al.* 2013).

Ionizing radiation (IR) is a well recognized although a relatively weak carcinogen (Burkart *et al.* 1997; Tubiana 2000) and radiogenic cancer is the most important stochastic (i.e., random) health effect of absorption by a human being of ≥100 mSv of IR (UNSCEAR 2000, 2008). Carcinogenesis is a complex, multi-step process beginning with the neoplastic transformation of a normal cell resulting from fixed mutations within a couple of special DNA fragments called oncogenes and tumour suppressor genes (Weinberg and Hanahan 2000). The transformed (*initiated*) cell, the so-called cancer stem cell, is capable of uncontrolled self-renewal (proliferation) which, in conducive circumstances, leads to the development of a clone (*promotion*) of dividing and/or maturating cells resistant to the adverse defence reactions of the surrounding normal tissue environment (Schreiber *et al.* 2011). Finally, some of the 'promoted' cells become malignant by acquiring the capacity to cross tissue barriers, and invade and proliferate into new cancer foci (metastases) in distant sites of the organism. The carcinogenic process therefore is not limited to the accumulation of mutations and disturbed regulation, rearrangement, deletions and duplications of genes, but also relies heavily on the suppressed or modified function of the proliferating cancer stem cells' microenvironment (Barcellos-Hoff 2005; Tubiana 2009). All these processes are time-consuming and, consequently, it usually takes several years or even decades for a set of neoplastically transformed cells to develop into a full-blown clinical cancer. IR is a known risk factor for many types of cancer, the most typical are leukaemias (except for chronic lymphatic leukaemia), which appear most rapidly (i.e., from about 2 years) after the exposure, and such solid tumours as cancers of the breast (in women), the thyroid gland, the urinary organs, the skin (other than melanoma), and the lungs; for these tumours the time from the initiation to the full-blown disease (*latency*) may take from several years to a few decades (BEIR VII 2006). Noteworthy, radiogenic malignancies do not differ either morphologically or clinically from cancers that develop in the same organs and tissues due to other causes or the activity of carcinogens (BEIR VII 2006; UNSCEAR 2008).

In children, the most common cancer is leukaemia[1], predominantly acute lymphoblastic leukaemia (ALL), although these diseases are relatively rare in childhood: depending on the country the incidence rates range from 1.5 to 5.0 per 100,000 (Stiller and Parkin 1996; WHO 2010). Molecular studies have revealed a two-stage origin of many childhood leukaemias: a preleukaemic stem cell clone (*initiation* and *promotion*) is thought to be generated *in utero* and, in a minority of children, the progress to the full-blown disease takes place after birth when a number of postnatal genetic and epigenetic alterations have set in (*progression*); as in many other malignant neoplasms the nature of pre- and post-natal

events involved in leukaemogenesis in children is not well understood (Rossig and Juergens 2008).

In spite of the fact that the dose rate of IR released to the environment is in the range of 0.0001 to 0.007 mSv/year (Strupczewski 2010; Lane *et al.* 2013), i.e., a very small fraction of the average natural background radiation (1 to 2 mSv/year), it is commonly believed that living in the vicinity of a NPP can be hazardous to human health. This opinion has been supported and fueled by various groups of 'ecologists' and also – unfortunately – by a few scientists who claim that not only disasters such as in Chernobyl and Fukushima, but even a normal, undisturbed operation of an NPP can cause ill health and deaths among the local people (Fairlie 2010, 2013; Nussbaum 2009).

Nuclear energy production has been triggering off social anxiety ever since the first NPPs started operations in the 1950s in the USA, USSR, and Great Britain. However, scientific analyses of a possible impact of the NPPs on human health, specifically the incidence of cancer, were first published as late as in the 1980s (Black 1984). Indeed, it were the Yorkshire TV journalists who in a programme aired in 1983 (Cutler 1983) reported on their discovery of seven cases of leukaemia (a leukaemia *cluster*) in young people under 25 years of age who from 1955 to 1983 lived in Seascale, a village on the coast of the Irish Sea in Cumbria, England, 3 km away from Sellafield[2] – the main British nuclear reprocessing site. The discovery of that 'Seascale cluster', as it has come to be called, seemed to be a most unusual happening since, according to the general incidence rate, the expected number of leukaemia cases among the young in that period of time should be less than one; hence, the excess was 10-fold with

[1]*Childhood leukaemia* is a type of childhood cancer. It is a hematological malignancy or a cancer of the blood. It develops in the bone marrow where new blood cells are made. Leukaemia is usually described either as 'acute', which grows quickly, or 'chronic', which grows slowly. Almost all childhood leukemia is acute. One main type of acute leukemia is *acute lymphocytic leukaemia* (ALL), which accounts for about 3 out of 4 cases of leukaemia in children. ALL is a form of leukaemia that affects the lymphocytes, a type of white blood cells which fight infection. Another type of acute leukaemia is *acute myelogenous leukaemia* (AML), a cancer of the blood in which too many myeloblasts, immature white blood cells, are produced in the bone marrow. The marrow continues to produce abnormal cells that crowd the other blood cells and do not work properly to fight infection. Chronic leukaemias are more common in adults and although they tend to grow more slowly than acute leukaemias, they are harder to treat. These chronic leukaemias are divided into two types: *chronic myelogenous leukaemia* (CML) and *chronic lymphocytic leukaemia* (CLL). CML is rare in children, but does occur and is treatable in children the same as in adults. Most childhood leukaemias are acquired genetic diseases. An alteration or defect in the immune system may increase the risk for leukaemia. The immune system can be damaged by different factors, such as exposure to viruses, environmental factors, chemical factors or ionizing radiation. Fortunately, the cure rate of childhood leukaemia is generally higher than adult leukaemia, approaching 90%.

[2]Sellafield is an off-shoot from the original nuclear reactor site at Windscale which has undergone decommissioning and dismantling.

p<0.001 (Urquhart *et al.* 1984). Shortly afterwards five excess cases in less than 24-year-olds (three of whom were <four years of age) were diagnosed in western Thurso, a small town on the north coast of the Highland council area of Scotland, 12.5 km from the NPP established in the mid-20th century at Dounreay, Scotland (Heasman *et al.* 1986). The third report came from Germany where in the beginning of the 1990s nine leukaemia cases were discovered among children under 10 years of age living in the community of Elbmarsch in northern Germany from 1989 to 1996 (Schmitz-Feuerhake *et al.* 1993; Hoffmann *et al.* 1997; Schmitz-Feuerhake *et al.* 1997); notably, only between February 1990 and May 1991 five cases of acute leukaemia (SIR[3] = 11.8; 95%CI[4], 4.9-28.3) were diagnosed (Hoffmann *et al.* 1997). All these children were living within approx. five km of the Krümmel NPP (*Kernkraftwerk Krümmel – KKK*), the largest boiling water reactor in the world started in 1983, located on the river Elbe about 35 km southeast of Hamburg. In 2007 Hoffmann *et al.* published the results of an ecological observation of childhood leukaemia diagnosed from 1990 to 2005 in <15-year-olds living within five km of the Krümmel NPP: during that period the ratio of the actually observed (O) to the expected (E) cases was O/E=14/4, which gave the SIR value of 3.5 (95%CI, 1.9-5.9); however, the greatest SIR value was calculated for the ill children less than four years old (SIR=4.9; CI, 2.4-9.0) (Hoffmann *et al.* 2007). Schmitz-Feuerhake and her colleagues postulated that the high rate of childhood leukaemia in the Elbmarsch region could be due to the release of radionuclides during an accident in the nuclear facility adjacent to the KKK in 1986 (Schmitz-Feuerhake *et al.* 2005). This suggestion was supported by the expert Committee of Schleswig-Holstein which concluded in their report that an accidental release of radioactivity was a likely cause of elevated SIR for childhood leukaemia (Wassermann *et al.* 2004). However, as indicated by Hoffmann and co-workers an accident in the nuclear facility near the KKK can be challenged because it is unlikely that such an accident could have escaped environmental surveillance, and no action by public authorities was taken (Hoffmann *et al.* 2007). Indeed, the expert commission empanelled by the Federal State of Lower Saxony, the administrative authority for the Municipality of Elbarsch, concluded that during normal operations of the nuclear facilities in Elbmarsch no association can be found between childhood leukaemia

[3]Standardized Incidence Ratio (SIR) - the observed total number of cases (O) in the study group, divided by the expected number of cases (E) based on the standard population rates applied to the study group.

[4]95% confidence interval, i.e. the range (interval) of values in which the investigator can be 95% confident that the true mean of the underlying population falls; CI alone can be used as a test to see whether a mean or proportion differs significantly from a fixed value: if the interval includes 1.0 the mean or proportion is not significantly different from 1.0 (Jekel *et al.* 2001).

and the radioactive emissions and suggested that not all local risk factors may have been identified (Wichmann and Greiser 2004).

In 1990 a publication in the British Medical Journal informed about an increased incidence of childhood leukaemia in the Nord Cotenin region in Normandy, France, where a couple of nuclear installations including the La Hague nuclear fuel reprocessing plant (the third such facility in the world operating on an industrial scale, the other two being Sellafield, England and Dounreay, Scotland) and the Flamanville NPP are located (Viel and Richardson 1990). During the period 1978-1990, a total of 23 cases of leukaemia were diagnosed in up to 25-year-old people living with a 35-km radius of the La Hague plant (SIR = 2.99) and three leukaemia cases were detected in the Flamanville 'canton' (SIR = 2.5); the two excesses, however, were statistically insignificant (Viel *et al.* 1993), as were the excesses registered between 1978 and 1992 in further studies of Viel and co-workers (Viel *et al.* 1995).

Extension of these analyses unto 1998 and taking account of the age of the subjects and cytological types of leukaemia also produced insignificant results (SIR = 2.17; 95% CI: 0.71, 5.07) for all the age groups and the whole of the Beaumont-Hague electoral ward, although a significant excess rate of ALL was noted for the five- to nine-year-old children (SIR = 6.38; 95%CI: 1.32, 18.65) (Guizard *et al.* 2001).

Although it has been well established that childhood leukaemia routinely clusters by chance in space and time (Petridou *et al.* 1996; McNally *et al.* 2002; Bellec *et al.* 2006; Amin *et al.* 2010) the above reports rightly exacerbated the general public's and scientific community's anxieties and interest mainly because: a) foetuses and children are most vulnerable to adverse effects of various environmental toxins, including IR (Doll and Wakeford 1997; WHO 2010), b) IR is an acknowledged 'risk factor' of leukaemia – a radiogenic neoplasm appearing the earliest post-exposure (Doll and Wakeford 1997; UNSCEAR 2000; BEIR VII 2006; Rossig and Juergens 2008; Wakeford 2008), and c) leukaemia is a very rare disease in children (Stiller and Parkin 1996; WHO 2010).

Epidemiological reports from the immediate vicinities of Sellafield, Dounreay, and Krümmel were the products of the so called 'ecological' ('geographical') descriptions which relate the frequency (in this case the incidence of leukaemia) with which some 'risk factor' (exposure to IR) and a possible outcome (childhood leukaemia) occur in the same geographic area (Jekel *et al.* 2001). Such studies are useful for suggesting hypotheses, but they cannot be used to draw *causal* conclusions, because there is no information as to whether individual subjects who had actually (and to a plausibly defined extent) been exposed (to IR) were the same people in whom the outcome (leukaemia) was diagnosed. The probability of the cause-effect relationship between the risk factor and the outcome can only be tested with the so called in epidemiology analytical

investigations, such as cohort studies (in which a defined group of people – a cohort – exposed to the risk factor under study are analyzed in terms of their disease incidence) or case-control studies (in which exposure to the risk factor of an identfied group of people with a certain disease likely to be caused by that risk factor – cases – are compared with the exposure of a group of subjects without the disease – controls) (Laurier and Bard 1999; Jekel *et al.* 2001). This probability is most often expressed in the former studies by the calculated 'relative risk' (RR) or 'excess relative risk' (ERR), and in the latter studies by the 'odds ratio' (OR) accompanied by their respective 95% confidence intervals (95%CI).

Hence, the descriptive reports of the leukaemia clusters in Seascale, Thurso, and Elbmarsch have naturally led to analyses of the potential association of the disease (predominantly leukaemia and non-Hodgkin lymphoma, but also other cancers in youngsters) with the exposure to IR associated with living in the vicinity of a nuclear installation. In the 1990s a number of such analyses were published from studies carried out in Canada, England, France, Germany, and Scotland (reviewed in Michaelis *et al.* 1992; Laurier and Bard 1999). The results, mostly from case-control studies, were not unequivocal: some of them indicated or suggested the statistically significant association between the diagnosed disease and the distance to the installation where the ill children were living, other demonstrated no such relationship (Laurier and Bard 1999; Nussbaum 2009). In some of those studies it was postulated, based on a hypothesis proposed by Martin Gardner who had studied the Seascale cluster, that the diseases were the result of the fathers' irradiation during their work at a nuclear facility before their child's conception (Gardner *et al.* 1990; Gardner 1991).

In view of this, the British, French, and German governments commissioned their experts to perform the more in depth analyses. Thus, the UK Committee on Medical Aspects of Radiation in the Environment (COMARE)[5] concluded in their report from 1996 that the level of radiation around Sellafield was at least 200 times too low to be the cause the Seascale cluster (COMARE 1996); this conclusion recapitulated earlier verdicts of COMARE from 1986, 1988, and 1989. In their 11th report from 2006 COMARE – in the wake of their yet another analysis of the available data – states that childhood leukaemias, especially acute lymphocytic leukaemia, tend to form clusters in time and space (the reasons of which are not clear) and that there is no convincing evidence indicating that clusters of leukaemia and other cancers in children residing around the British nuclear installations are caused by the exposure to IR emitted from these installations (COMARE 2006). In Germany, a large-scale case-control study

[5]The UK-wide advisory committee established in 1985 'to assess and advise Government and the devolved authorities on the health effects of natural and man-made radiation and to assess the adequacy of the available data and the need for further research.'

was commissioned in 2002 to estimate the incidence of leukaemias and other cancers diagnosed between 1980 and 2003 in youngsters living in the vicinity of all 16 German NPPs. Because in this analysis, which has come to be known as the KiKK study (from German *Krebs bei Kindern in der Umgebung von Kernkraftwerken* – cancer in children in the vicinity of NPPs), individual radiation exposures of the 'cases' (1,592 up to five-year-old children at diagnosis living within <five or <10 km from the nearest NPP) as well as of 'controls' (4,735 appropriately matched children residing >10 km from the NPPs) could not be the estimated distance to the likely point of radiation emissions – the exhaust stack of the nearest NPP (with an accuracy of within 25 m) was used as a 'surrogate of the dose.' Results of the KiKK study showed that living within <five km or within <10 km from the nearest NPP coincides with the enhanced probability of developing cancer, especially leukaemia, in up to five -year-old children: depending on the way of modelling of the distance from the NPP the OR values for the <five km and <10 km distances ranged from 1.12 to 1.76 ('continuous' model) and from 1.33 to 2.19 ('categorical' model), respectively; in all the cases the 95%CI lower limits were >1.0, indicating statistical significance of the results (Kaatsch *et al.* 2008a; Spix *et al.* 2008). However, the SIR values calculated by the same authors were not statistically significant: for the <five km zone SIR of 1.41 (95% CI, 0.98-1.97) and for the five to <10 km zone SIR of 0.97 (95%CI, 0.74-1.25) were obtained (Kaatsch *et al.* 2008b). The undisputed strength of the KiKK study is that it was based on the greatest available number of relevant disease cases from all German NPP regions (37 cases of leukaemia cases among up to five-year-old children from the five-km zone out of total 593 cases of leukemia diagnosed in the study's 24-year period) and that it used individual measurement of residential proximity to the nearest NPP for each subject (as opposed to the previous ecological studies based on aggregate data) Noticeably, however, as indicated by its authors (Kaatsch *et al.* 2008a; Spix *et al.* 2008), the study had also significant limitations, the most important of which are: a) incomplete and error-prone recruitment of the controls which might have led to overestimation of the effect, b) no account for confounders such as, e.g., social status of the residents (a condition which favours the development of leukaemia in children), c) only residential addresses at the time of diagnosis were used to determine the distance to the nearest NPP, while previous addresses as well as the time spent with grandparents, in crèches, with childminders, on holiday, etc. were disregarded, d) natural background radiation whose variation in Germany is >1000 times greater than radiation exposure from any NPP in normal operation[6] was not taken into account; e) adoption by the authors

[6]For a 50-year-old citizen in 1991 living within 5 km of one of the German NPPs, the expected cumulative dose from atmospheric discharges would range from 0.0019 (Obrigheim) to 0.32 μSv (Gundremmingen) (Smith *et al.* 2002).

of the BEIR Committee's view that a beneficial effect of radiation cannot be expected even at extremely low doses (BEIR VII) as the basis for the use in the statistical analyses of one-tailed tests which, in contrast to the two-tailed tests, are more prone to detect a significant difference, if it is in the *expected* direction (Jekel *et al.* 2001; Dallal 2012). The critical review of their own studies led the authors to conclude that the results are 'not to be expected under current radiation-epidemiological knowledge and considering that there is no evidence of relevant accidents and that possible confounders could not be identified, the observed positive distance trend remains unexplained' and that 'we cannot exclude the possibility that this effect is the result of uncontrolled confounding or pure chance' (Kaatsch *et al.* 2008a; Spix *et al.* 2008).

The 'unexpected' and 'unexplained' results of the KiKK study have not been substantiated or supported by other extensive analyses. In 1999 Dominique Laurier and Denis Bard reviewed the hitherto effectuated 29 local and 14 'multi-site' (intended to test on a global basis the increase in the frequency of the leukaemia near all the nuclear sites of a region or a country) descriptive and seven case-control studies of leukaemia incidence among young people living near nuclear facilities (Laurier and Bard 1999). The results indicated that: a) although descriptive (ecological) studies showed the existence of clusters of childhood leukaemia near some nuclear installations, this was not a general rule and the clusters were also observed far from any nuclear site, and b) the case-control (analytical) studies set up to search for the causes of such excesses near nuclear sites did not provide a definitive explanation for the clusters observed, but resulted in the rejection of some hypotheses (in particular those related to paternal pre-conceptional irradiation and to environmental exposure to IR). Likewise, a later analysis of Laurier and her colleagues of an increased risk of leukaemia in children around 198 nuclear sites in 10 countries (including 25 major multisite studies published for eight countries) concluded that although some clusters of childhood leukaemia cases exist locally the results based on multi-site studies do not indicate an increased risk among the young (up to 24 years of age) people living close to nuclear sites (Laurier *et al.* 2008a). According to these authors the main limit to determine the cause(s) of the excess of leukaemia cases observed locally is 'the lack of knowledge about the risk factors of childhood leukaemia', but the most convincing is the hypothesis of population mixing in the areas around nuclear sites (see below). Noticeably, even the 'independent' researchers who stick to the opinion that increased incidence of cancers among young inhabitants of regions surrounding nuclear installations are caused by IR emitted from these installations admit that in the 'large majority' of epidemiological studies demonstrating such increases the results are not statistically significant (Fairlie and Körblein 2010; Fairlie 2013). Indeed, the lack of the *substantially* increased (if any) risk of child-

hood leukaemia near nuclear facilities was demonstrated by several publications between 1991 and 2008 from studies of single or multiple NPPs and other nuclear sites in Israel (Sofer *et al.* 1991), USA (Jablon *et al.* 1991; Talbott *et al.* 2003), Sweden (Waller *et al.* 1995), Germany (Kaatsch *et al.* 1998), Japan (Yoshimoto *et al.* 2004), and France (Laurier *et al.* 2008b).

Finally, results of a recent case-control study from France (Sermage-Faure *et al.* 2012), of a nationwide cohort study from Switzerland (Spycher *et al.* 2011), the so called CANUPIS study, of yet another analysis of the British COMARE (COMARE 2011), and one large ecological observation from Canada (Lane *et al.* 2013), the RADICON study, do not provide evidence of the association between residence near NPPs and the risk of leukaemia or any other cancer in children. Interestingly, the latter study demonstrated that within 25 km of the three NPPs tested in Ontario the incidence of all childhood cancers, leukaemia and non-Hodgkin lymphoma from 1990 to 2008 in children aged zero to four years was *lower* than in the general Ontario population, although not statistically so, and cancer incidence in children aged 0-14 years was similar to the Ontario population: overall, the patterns of incidence of all cancers combined as well as of *radiosensitive* cancers were found to be within the natural variation of cancer rates in Ontario. In addition, the authors of that study, who used two different methods of dose estimation, demonstrated that exposure to radiation *increased* (to a certain limit) rather than decreased with the distance from the NPP indicating that such a distance used in many studies as a surrogate of the dose may not adequately reflect the actual radiation exposure (Lane *et al.* 2013).

There are also interesting results of some American and British investigations carried out in regions before and after a nuclear facility began operation. For example, Jablon and co-workers analyzed 62 nuclear sites in the USA and found that standardized mortality ratios (SMRs) for childhood leukaemia diagnosed in the zero- to nine-year-olds were higher before than after the start-up (SMR = 1.03 vs. SMR = 1.08); also, for the four facilities where incidence data were available (which, in the case of childhood leukaemia is a preferred indicator of the effect), three sites had higher SIRs after the beginning of operation, although rates were >1.0 for both periods (Jablon *et al.* 1991). Likewise, Cook-Mozaffari and co-workers who analyzed mortality from leukaemia and other cancers in England and Wales found that the excess cancer death rates in regions that already had a nuclear facility were similar to those in regions only considered for the installation (Cook-Mozaffari *et al.* 1989). Also, the 14th COMARE report revealed that in zones near 13 British NPPs the relative risk (RR) of leukaemia or non-Hodgkin lymphoma in children aged zero to four years was equal to 1.01 (95%CI, 0.70-1.47), whereas in six possible locations for NPPs where no installation was constructed the risk equaled to 1.72 (95%CI, 1.12-2.52) (COMARE 2011).

In summary, the reviews of the reliable investigations published thus far indicates that childhood clusters around nuclear installations have been detected only in three locations: near Sellafield in England, near Dounreay in Scotland, and near Krümmel in Germany (Lane *et al.* 2013). Because, however, as has been repeatedly demonstrated, exposure to IR is not the underlying causative factor, a plausible explanation(s) for these clusters has been persistently sought over the years. Obviously, many acknowledged or suspected causes have been taken into account. These potential causes and/or conducive conditions include genetic predisposition (Birch 1999; Lichtenstein *et al.* 2000), prenatal exposure to clastogens, tobacco smoke, pesticides, some drugs, and/or viruses (Bithel *at al.* 1973; Blot *at al.* 1980; Golding *et al.* 1990; Doll and Wakeford 1997; Rossig and Juergens 2008), trisomy 21, the cause of approximately 95% of observed Down syndromes (Robinson 1992), high socioeconomic status (Alexander *et al.* 1991; Rossig and Juergens 2008), some medications (Lichtenstein *et al.* 2000), and a defective function of the immune system in response to infections (Greaves 2006); in 75-90% of the cases, however, the real causes remain unknown, and most probably, several factors must play in concert or in a sequence to lead to the development of the disease (Anderson *et al.* 2000; Lichtenstein *at al.* 2000; Greaves 2006; Rossig and Juergens 2008). It has been suggested that in children mechanisms of metabolizing and/or scavenging of environmental toxins are less effective than in adults and there are 'critical time windows' during which external factors are more likely to cause damage and evoke disease (Anderson *et al.* 2000; WHO 2010). As mentioned earlier, one of the hypotheses proposed after the detection of the 'Seascale cluster' was a pre-conceptional exposure of fathers of leukaemic children during their employment at nuclear facilities (Gardner *et al.* 1990; Gardner 1991). However, a number of analyses (Urquhart *et al.* 1991; Kinlen 1993; Parker *et al.* 1993; Draper *et al.* 1997; Pobel and Viel 1997) revoked the Gardner's hypothesis mainly because fathers occupationally exposed to radiation were employed in many different nuclear facilities across England, but the significant excess of childhood leukaemia cases was detected only in Seascale in the Cumbria county. Also, no support for the pre-conceptional paternal irradiation has come from studies of the offspring of atomic bomb survivors in Hiroshima and Nagasaki, or of nuclear workers in various parts of the world (COMARE 2002). Obviously, one of the reasons for the 'Seascale' and other similar clusters, therefore, can be the known tendency of childhood leukaemia to 'spontaneously' aggregate in time and space (Kaatsch *et al.* 2010; Greaves 2006).

Even a more probable cause was proposed already in 1988 by Leo Kinlen who analyzed the incidence of leukaemia among young residents of the New Town of Glenrothes which in the 1950s received a large influx of workers from other parts of the country (*incomers*) in association with

its development as a new Scottish industrial centre (Kinlen 1988). Such an influx of strangers (*population mixing*) promotes a spread of the dragged infectious agent(s) among the local population. Indeed, the industrial centre was built in an unusually isolated place where herd immunity[7] to a postulated virus infection (to which leukaemia is a rare response) would tend to be lower than average. In fact, Kinlen found a significant increase of leukaemia cases in young (<25-year-old) residents of the Glenrothes region (10 observed vs. 3.6 expected cases), with the greatest excess in children up to five years of age (7 observed vs. 1.5 expected) (Kinlen 1988). This 'population mixing' hypothesis was confirmed by significant excesses of leukaemia and non-Hodgkin lymphoma cases found in 1979-1983 in the group of rural areas were large oil terminals were constructed in the Shetland and Orkney islands (Kinlen *et al.* 1993; Kinlen *et al.* 1995), by a thorough analysis of 119 539 children born between 1969 and 1989 to mothers living in Cumbria (excluding Seascale) indicating that population mixing is a significant factor for acute lymphoblastic leukaemia and non-Hodgkin lymphoma, especially in young children (Dickinson and Parker 1999) as well as by similar results of 12 further studies of non-radiation situations in six countries and three nuclear sites (Kinlen 2011). These observations are compatible with the currently held view that an abnormal immune response during delayed exposure to common infections provides a plausible mechanism for malignant progression of pre-leukaemic clones in a subgroup of susceptible children (Rossig and Juergens 2008). No wonder, therefore, that a renown British epidemiologist, Sir Richard Doll proposed in his 1999 Editorial in the British Journal of Cancer that "the time may now have come when Kinlen's hypothesis of population mixing as a cause of childhood lymphatic leukaemia can be regarded as established (Doll 1999).

CONCLUSION

A number of reliable analyses have clearly indicated that radiation exposure of populations residing in the proximity of NPPs is much too low to account for the increased number of leukaemia and other cancer cases discovered among young members of a few such populations. The most likely explanation for these discoveries, especially of the childhood leukaemia clusters, is the influx from outside of workers to the newly industrialized rural regions (the usual places for NPPs to be set up) where

[7] *Herd immunity* describes the proportion of subjects with immunity to infection in a given population (herd). This definition dissociates herd immunity from the indirect protection observed in the unimmunized segment of a population in which a large proportion is immunized, for which the term 'herd effect' is proposed. It is defined as: 'the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population'. (John and Samuel 2000).

local people were not immune to viruses brought along with the incomers. Certainly, other possible leukaemogenic and conducive factors must also be taken into account including the well acknowledged tendency of childhood leukaemia to form 'spontaneous' clusters in time and space. Indeed, advancing our knowledge about cancer risks in children living near nuclear facilities will require further studies focused on, among other things, *in utero* and early childhood exposures, use of specific geographic and dosimetric information, consideration of pathways for transport and uptake of radionuclides, and last but not least designed so as to directly address causal hypotheses regarding cancer risk near nuclear facilities (Wing *et al.* 2011). It can only be hoped that new such studies, e.g. the one commissioned by the National Research Council of the National Academies (NRC 2012) which, based on the results of the reconnaissance Phase 1 investigation recommends carrying out two complementary studies (an ecologic and a record-based case-control study) with the analysis based on maternal residence at time of delivery of the child as a more appropriate way of capturing relevant exposures will address some of the most pertinent and unresolved issues and provide better insights into the causes of childhood cancers in populations neighbouring on NPPs.

Regardless of the results of the future studies it can already be responsibly asserted that a lifetime residency close to a normally operating modern NPP does not pose any specific health risk to people, and certainly that IR emitted thereof cannot cause cancer. What's more, even the greatest nuclear accident that happened in 1986 at the Chernobyl NPP, accompanied by the massive release of radiation and radionuclides to the environment, has not resulted in the increased incidence of leukaemia and other neoplasms (with the only exception of thyroid cancers in those who were below 18 years of age at the time of the catastrophe and accumulated >100 mGy of radiation from I-131 in their thyroid glands) among the populations of even the most contaminated regions of Belarus, Ukraine, and Russia, including the local children who were exposed to radiation before and after birth (UNSCEAR 2008).

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